UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/010,763	11/02/2001	Isaiah J. Fidler	UTSC:684US/SLH	2999

7590 11/09/2004

FULBRIGHT & JAWORSKI L.L.P.
A REGISTERED LIMITED LIABILITY PARTNERSHIP
SUITE 2400
600 CONGRESS AVENUE
AUSTIN, TX 78701

EXAMINER	
UNGAR, SUSAN NMN	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 11/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/010,763	FIDLER ET AL.	
	Examiner	Art Unit	
	Susan Ungar	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *02 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) *3-7 and 15-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1,2 and 8-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/30/, 2/20, 2/14/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. The Election filed September 2, 2004 in response to the Office Action of July 6, 2004 is acknowledged and has been entered. Claims 1-33 are pending in the application and Claims 3-7, 15-33 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions. Claims 1-2, 8-14 are currently under prosecution.

2. The response to the restriction requirement of July 6, 2004 has been received. Applicant has elected Group 1, claims 1-2, 8-14 for examination with traverse. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP 818.03(a).

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-2, 8-14 are rejected under 35 USC 112, first paragraph because the specification, while being enabling for a method of determining the effectiveness of a cancer treatment/prostate cancer treatment comprising determining growth factor receptor/EGFR phosphorylation in a tissue sample obtained by non-invasive procedures, wherein said cancer expressed growth factor receptor/ EGFR prior to treatment and wherein said treatment specifically targets the growth factor receptor/EGFR receptor, does not reasonably provide enablement for a method of determining the effectiveness of therapy to

treat a cancer/prostate cancer by determining growth factor receptor/EGFR phosphorylation in a tissue. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The claims are drawn to a method of determining the effectiveness of a cancer treatment comprising determining growth factor receptor/EGFRphosphorylation in a tissue sample obtained by non-invasive procedures. This means any and all cancers, regardless of whether or not they expressed EGFR protein prior to treatment. The specification teaches that tumor cells generally express more growth factor receptors than normal cells and that chemotherapeutic drugs typically used to treat cancers and their metastases are those that inhibit phosphorylation of the growth factor receptors and include C225 antibody that inhibits phosphorylation of the EGFR (page 2, lines 25-31). Tissue sample types that may be obtained by non-invasive methods include hair follicle cells, buccal mucosa cells, skin scrapings, bladder wash cells, pap-smear samples (p. 3, lines 15-17). The control herein is the amount of growth factor receptor in the sample before the cancer treatment (p. 3, lines 22-25). Non-invasive means procedures are defined herein as procedures that do not require surgery (p 4, lines 9-10). Applicant exemplifies a method of assaying EGFR phosphorylation from hair follicle wherein parallel expression level of activated EGFR is found both in neoplasms and hair follicles wherein the cancer treatment used targets the EGFR receptor (p. 8, lines 3-5). Applicant teaches that several tumor cell types have been found to express much more growth factor receptors than normal cells and that these receptors are phosphorylated in cancers. Applicant specifically teaches that EGFR has been shown to be highly expressed in human pancreatic tissues wherein

administration of PK1166, an EGFR phosphorylation inhibitor, to nude mice results in dramatic shrinkage of metastases of human cancer cells and a reduction in phosphorylated EGFR levels and the present invention takes advantage of this finding to provide a non-invasive method for determining the effectiveness of anticancer agents in treating tumors and metastases (p. 8, lines 18-27). In addition, according to the invention, a sample of EGFR expressing cells is collected from a patient suffering from a form of cancer which is known to overexpress EGFR prior to treatment and the level of phosphorylation is determined by known methods (p. 9, lines18-30), wherein methods for detection of phosphorylated growth factor receptor are well known in the art (p. 11, lines 4-15), wherein Applicant exemplifies the parallel expression of activated EGFR in Neoplasms and Hair Follicles (see Example 3, pages 60) wherein the exemplified method is not commensurate in scope with the claimed invention because the sample tested is excised (that is by surgical methods, from the skin of the mice used in the experiments).

One cannot extrapolate the teaching of the specification to the scope of the claims because the claims are drawn to (1) assessing the efficacy of any type of therapy for prostate cancer in any tissue, (2) regardless of whether the primary tumor expresses EGFR. This means determining the efficacy of a treatment not related to anti-growth factor receptor/EGFR therapy, in any tissue.

(1) In particular, the specification makes clear that assay for receptor phosphorylation can be done in a variety of tissues not associated with the tumor being treated. Exemplification of this limitation is drawn only to assay of tissues after pan treatment with anti-EGFR phosphorylation inhibitor, which would be expected to inhibit EGFR phosphorylation throughout the patient's body.

However, it would be also be expected, that if the treatment had been directed to another growth factor receptor, or a different type of molecule altogether, there would not be any influence on the phosphorylation of EGFR.

(2) In particular, it is not clear from the information in the specification how one would go about determining whether therapy had been successful if the cancer never expressed a growth factor receptor/EGFR. Certainly, the specification makes clear that not all cancer types express all growth factor receptors/EGFR (page 8) and further specifically states that the invention is drawn to a patient suffering from a form of cancer which is known to overexpress EGFR prior to treatment (see page 9). lt certainly would not be expected that assay for growth factor receptor/EGFR in the cancer types that do not express the growth factor receptor/EGFR could be successfully assessed for the efficacy of therapy by assaying for growth factor receptor/EGFR phosphorylation.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention could function as currently claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

Claim Rejections - 35 USC § 103

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to

which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-2, 8-14 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Pollack et al (Proc. Annu Meet AACR, 1997, 38(A4249) or Pollack et al, (J. Pharm Exp. Ther., 1999, 291:739-748, IDS item, publicly available October 19, 1999), in view of Scardino et al (NCI monographs, 1988, 7:95-103), Prewett et al (J. Immunotherapy with Emphasis on Tumor Immunology, 1996, 19(6)419-427) and Prewett et al (Clin. Can. Res., 1998, 4:2957-2966).

It is noted that the specification specifically states that antibody methods of assessing phosphorylation of growth factor receptors were conventional and well known in the art at the time the invention was made including anti-phosphoprotein antibodies as well a labels for detecting said antibody wherein detection can be by the labeling of the first binding antibody or by the binding of a secondary antibody that is then detected by means of the detectable label (page 11), and given that Applicant admits the conventionality of the known assays, claims 8-13 are obvious for any method of detecting phosphorylated growth factor receptors.

It is noted for examination purposes that needle biopsies are not invasive procedures as defined by the specification because they do not involve surgery (see page 4 of the specification).

The claims are drawn to a method of determining the effectiveness of a cancer treatment comprising obtaining a tissue sample by non-invasive procedures from a patient undergoing cancer treatment and determining growth factor receptor phosphorylation in said tissue before and after the cancer treatment (claim 1), wherein phosphorylation of an EGFR is determined (claim 2), wherein determining said growth factor receptor phosphorylation comprises obtaining a sample

comprising said growth factor receptor, contacting said receptor with an anti-phosphorylated growth factor receptor antibody and detecting said antibody (claim 8), wherein said antibody comprises a detectable label (claim 9), wherein a second antibody that comprises a detectable label is contacted prior to detection (claim 10), wherein said detectable label is selected from a group including a fluor, an enzyme or a radionucleide (claim 11), wherein said detecting comprises immunofluorescence (claim 12), colorimetric detection (claim 13), wherein said patient has prostate cancer (claim 14)

Pollack et al (AACR) specifically teaches that tyrosine phosphoylation of EGF receptors is an important early event in signal transduction and tumor cell replication, wherein an *ex vivo* assay to quantitate EGFR-specific tyrosine phosphorylation in human tumors obtained as sc zenografts in athymic mice, ELISA, was used to determine the extent and duration of drug action *in vivo*, wherein it was found that CP-358774 is an effective inhibitor of EGFR tyrosine phosphorylation and it produces 70% inhibition of EGFR phosphorylation over a 24 hour period and that this inhibition of EGFR phosphorylation in the *ex vivo* assay effectively correlates with the potency and degree of inhibition of EGFR-dependent human HN5 tumor growth, known to overexpress active, phosphorylating EGFR, in a xenograft therapy model, suggesting that CP-358774 may be an important agent for therapy of EGFR-overexpressing human cancers. Given the above, it is clear that the tumor cells were assayed for EGFR phosphorylation, prior to treatment. Given the admission, on the record, of the conventionality of phosphoprotein assays, the claims 8-13 are clearly obvious in view of the method of Pollack et al.

Pollack et al, IDS item, specifically teaches that tyrosine phosphoylation of EGF receptors is an important early event in signal transduction and tumor cell replication, wherein an *ex vivo* assay to quantitate EGFR-specific tyrosine phosphorylation in human tumors obtained as sc zenografts in athymic mice, ELISA, was used to determine the extent and duration of drug action *in vivo*. It was found that CP-358774 is an effective inhibitor of EGFR tyrosine phosphorylation and it produces 70% inhibition of EGFR phosphorylation over a 24 hour period (see abstract). This inhibition of EGFR phosphorylation in the *ex vivo* assay effectively correlates with the potency and degree of inhibition of EGFR-dependent human HN5 tumor growth in a xenograft therapy model, known to overexpress active, phosphorylating EGFR (p. 741,col 2, results), suggesting that CP-358774 may be an important agent for therapy of EGFR-overexpressing human cancers (p. 747, col 2). Given the above, it is clear that the tumor cells were assayed for EGFR phosphorylation, prior to treatment. Given the admission, on the record, of the conventionality of phosphoprotein assays, the claims 8-13 are clearly obvious in view of the method of Pollack et al.

Pollack et al teach as set forth above, but do not teach said method of assaying effectiveness of treatment for prostate cancer, for prostate cancer wherein a tissue sample is obtained by non-invasive procedures from said patient.

Scardino et al teaches conventional needle biopsy of prostate tumors for the determination of efficiency of therapy in a prostate cancer patient.

Prewett et al, 1996, teach that a correlation exists between overexpression of EGFR and poor clinical prognosis, wherein antibody C225 was used to treat prostate carcinoma xenografts in nude mice wherein it was determined that antibody C225 blocks EGF-induced receptor activation and that *in vivo* treatment

with C225 significantly inhibited prostate tumor progression in nude mice and suggests that the drug may have utility for the treatment of human prostate carcinoma in a clinical setting(see abstract).

Prewett et al, 1998 teaches that antibody C225 inhibits ligand-stimulated tyrosine phosphorylation of EGFR (see abstract).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the methods of Pollack et al, AACR or Pollack et al, IDS with the methods of Prewett et al, 1996/98 in order to determine the effectiveness of the C225 treatment, that is in order to determine the extent and duration of drug action *in vivo* because Prewett et al, 1996 specifically teaches that C225 is an effective antagonist of EGFR activation and suggests that the drug may have utility for the treatment of human prostate carcinoma in a clinical setting and Prewett et al, 1998 specifically teaches that the antagonism is by inhibition of phosphorylation of the EGFR receptor. Further, it would have been *prima facie* obvious to one of ordinary skill in the art to combine the methods of the combined references with the conventional needle biopsy method of Scardino et al in order to get information drawn to the efficiency of the therapy by a conventional method. One would have been motivated to combine the methods of the cited references in order to further characterize a treatment for prostate cancer.

7. No Claims allowed

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (571) 272-0837. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at 571-272-0787. The fax phone number for this Art Unit is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 872-9306.

Susan Ungar
Primary Patent Examiner
November 3, 2004